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THE EFFECT OF ANESTHETIC AGENTS ON EVOKED CENTRAL NERVOUS SYSTEM RESPONSES

Muscle Relaxants and Volatile Agents

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IN A previous paper (1), the depressant effects of gaseous anesthetic agents on evoked potentials in the postero-ventrolateral nucleus of the thalamus and the periaqueductal reticular formation of the cat midbrain from peripheral nerve stimulation have been described. This work was based on the original paper of French, Verzeano and Magoun (2) describing the reversible effects of ether and nembutal on the midbrain reticular formation. The present study is an extension of that work and is concerned with the effect of the commonly used muscle relaxants and volatile anesthetic drugs on somatic afferent evoked potentials from the same brain regions. The continuation of this study was undertaken to provide further qualitative and quantitative information on the action of additional anesthetic agents on lemniscal and extralemniscal afferent pathways as well as to rule out possible alteration of the results by muscle relaxants.

METHOD

A detailed description of the experimental technique has been reported previously (1). Briefly, cats were anesthetized with cyclopropane, atropine 0.2 mg./kg. administered hypodermically, a tracheotomy performed, a femoral vein and artery cannulated, and the brain exposed through a partial hemicraniectomy. A bipolar electrode was

This study was presented on the "Work in Progress" program at the Annual Meeting of the American Society of Anesthesiologists in Los Angeles, California, October 18, 1957 (ANESTHESIOLOGY 19: 98, 1958), and accepted for publication March 3, 1958. Dr. Davis is Associate Professor of Anesthesiology; Dr. Dillon was formerly Resident in Anesthesia (present address: 910 Medical Arts Bldg., Salt Lake City 11, Utah); Dr. Collins is Assistant Professor of Neurosurgery; Dr. Randt is Associate Professor of Neurology; all of Western Reserve University School of Medicine, Cleveland 6, Ohio.

applied to the exposed contralateral superficial radial nerve. After placing the animal in a stereotaxic instrument, the cyclopropane was withdrawn and needle electrodes insulated to within 45 to 150 microns of a 15 micron tip were placed in the postero-ventrolateral (PVL) nucleus of the thalamus (Horsley-Clarke coordinates: F 7, L 6, HC −1) and the periaqueductal reticular formation of the midbrain at the approximate level of the superior colliculus (F 2, L 2, HC 0) (3). Adjustments were made to obtain maximal evoked potentials at each site. Histological verification of the electrode placements was obtained by the method of Marshall (4) following the experiments.

The smallest dose of the selected muscle relaxant which would prevent undue movement was given. The relaxant which was to be studied subsequently was used so as to avoid possible interaction of two drug effects. The hind limbs and trunk were elevated to support blood pressure and the animal ventilated by means of a Mautz respirator (5), using a to-and-fro carbon dioxide absorption system. Arterial blood pressure, electrocardiogram, and rectal temperature were monitored.

Following electrode placement, 1.0 to 3.0 volt single stimuli were applied to the contralateral superficial radial nerve every three seconds and the potentials evoked in the thalamus and midbrain were amplified and projected on a synchronized dual beam oscilloscope where they were photographed. A control period was observed until constant potentials were recorded.

The muscle relaxants were then given rapidly intravenously. Following administration of the initial dose, a series of consecutive potentials were recorded at intervals of 30 seconds, 1 minute, 2 minutes, 3 minutes, 4 minutes, 5 minutes, and thereafter every 2 minutes until at least 10 minutes had elapsed. Subsequent increasing doses were given and recordings made in a similar manner until a predetermined maximum dose was reached. Following completion of these observations, the preparation was used for the study of the effects of a volatile agent.

The volatile agents were applied in varying concentrations in oxygen by manual positive pressure breathing using a Stephen-Slater nonrebreathing technique. The desired concentrations, corrected to room temperature and local barometric pressure, were obtained by volatilizing a known volume of liquid agent with a known volume of oxygen into a large latex reservoir bag (6). The oxygen source was a standard Foregger rotameter anesthesia machine recalibrated for accuracy. The mixture was then fed into the tail of a 2-liter breathing bag from which it was applied to the cat.

Resultant potentials were photographed at the above described time intervals up to 15 minutes; in one or two instances, this interval was extended beyond 20 minutes. At this time, 100 per cent oxygen was substituted and potentials recorded at 1 to 2 minute intervals up to 10

minutes, and at 3 to 5 minute intervals thereafter until control levels of response had returned. Because of the relatively prolonged effects of these agents, it was customary to study only one volatile agent in any one animal although, in certain instances, a second anesthetic was studied after a suitably long wait established the previous control potentials in that animal.

Hypotension, hypoxia, and hypothermia were carefully avoided because of their known depressant effects on the regions being studied. Animals in whom these variables could not be controlled were excluded from results.

Results

Muscle Relaxants.—Thirty-two cats made up this group. The results are summarized in table 1. The responses to the four agents

TABLE 1

Effect of Muscle Relaxants on Subcortical Evoked Central Nervous System Responses in Cat

Agent	Dose mg./kg. I.V.	Number of Animals	Site of Recording of Evoked Potentials	Changes in Evoked Responses		Effect on Blood Pressure	Clinical Dose Range (Man) mg./kg. I.V.
				Amplitude	Latency		
d-tubocurarine chloride	0.5–20.0	9	Thalamus PVL nucleus	No change when BP. maintained	0	Moderate to severe drop	0.1–0.3
			MB.-periaqueduct. Retic. Form.	No change when BP. maintained	0		
Gallamine triethiodide (Flaxedil)	2.0–32.0	6	Thalamus PVL nucleus	0	0	0	1.0–2.0
			MB.-periaqueduct. Retic. Form.	0	0		
Succinylcholine chloride (Anectine)	0.5–32.0	6	Thalamus PVL nucleus	0	0	0	0.5–1.0
			MB.-periaqueduct. Retic. Form.	0	0		
Decamethonium bromide (Syncurine)	0.4–4.0	11	Thalamus PVL nucleus	0	0	Occasional mild drop	0.03–0.05
			MB.-periaqueduct. Retic. Form.	0	0		

were all similar and the tracings showing the effects of *d*-tubocurarine in figure 1 are considered representative. Only one of the relaxants was used in each animal.

d-Tubocurarine Chloride: Nine cats were studied. In the dose range of 0.5 to 20.0 mg./kg. intravenously, *d*-tubocurarine showed no consistent changes in the amplitude, background activity, or conduction latency of the evoked potentials in the thalamus or the midbrain *provided hypotension was prevented.* Significant depression of the potentials, particularly from the midbrain, accompanied hypotension and could be reversed by blood pressure recovery. Such hypotension was commonly seen with *d*-tubocurarine in spite of prophylactic eleva-

tion of the legs and trunk; it could be controlled effectively by means of an infusion of norepinephrine (Levophed), 4 mg. of the base in 250 cc. of dextrose 5 per cent in water. In like manner, it has been previously observed that hypoxia will rapidly depress these potentials. This was avoided in all instances.

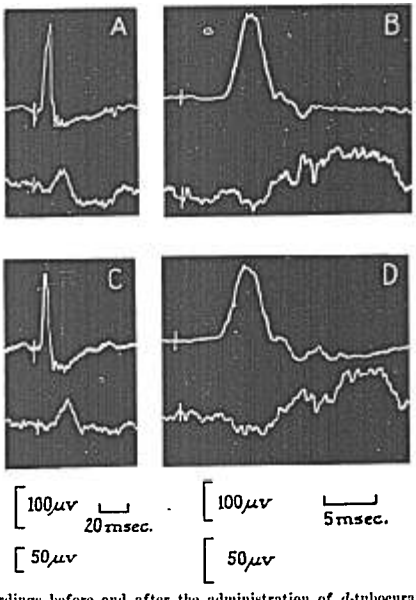

FIG. 1. Recordings before and after the administration of *d*-tubocurarine hydrochloride intravenously in the cat. The upper tracing of each photograph is from the postero-ventro-lateral nucleus of the thalamus, the lower from the midbrain periaqueductal formation at the level of the superior colliculi.

A and B are controls for C and D at slow and fast beam speeds, respectively, the latter to facilitate measuring of conduction latencies. C was taken 3½ minutes after, and D, 6 minutes after, *d*-tubocurarine 4 mg./kg. The time and amplitude calibrations vary for slow and fast beam tracings; the calibrations for A and C are on the lower left; those for B and D are on the lower right. In each instance, the 100-microvolt scale refers to the thalamic tracing, the 50-microvolt scale refers to the midbrain. The time calibrations for the slow and fast beams are indicated on the lower left and lower right, respectively.

GALLAMINE TRIETHIODIDE (FLAXEDIL): Six cats were studied. In the dose range of 2.0 to 32.0 mg./kg., gallamine produced no consistent changes in the amplitude, background activity, or conduction latency of the evoked potentials in either the thalamus or the midbrain. Hypotension was not encountered with this drug.

SUCCINYLCHOLINE CHLORIDE (ANECTINE): Six cats were studied. In the dose range of 0.5 to 32.0 mg./kg., succinylcholine showed no consistent changes in the amplitude, background activity, or conduction latency of the evoked potentials in the thalamus or the midbrain. Hypotension was not encountered.

DECAMETHONIUM BROMIDE (SYNCURINE): Eleven cats were studied. In the dose range of 0.5 to 4.0 mg./kg., decamethonium showed no consistent changes in the amplitude, background activity, or conduction

TABLE 2

EFFECT OF VOLATILE ANESTHETIC AGENTS ON SUBCORTICAL EVOKED CENTRAL NERVOUS SYSTEM RESPONSES IN CAT

Agent	Concentration Per Cent V/V	Number of Animals	Site of Recording of Evoked Potentials	Average Changes in Evoked Responses				Clinical Conc. Per Cent (Man) V/V
				Onset of Suppression (minutes)	Maximal Suppression		Recovery to Control (minutes)	
					Minutes	Per Cent		
Divinyl ether	8	5	Thalamus PVL nucleus	4	10	26	5	2–4
			MB.-periaqueduct. Retic. Form.	2	11	60	10	
Ethyl ether	10	5	Thalamus PVL nucleus	8	12	25	12	3.5–10
			MB.-periaqueduct. Retic. Form.	2	11	75	42	
Chloroform	2	4	Thalamus PVL nucleus	4	8	23	9	0.14–1.57
			MB.-periaqueduct. Retic. Form.	2	6	63	11	
Trichlor-ethylene	2	5	Thalamus PVL nucleus	5	11	20	6	0.5–2.0
			MB.-periaqueduct. Retic. Form.	1	7	40	11	

latency of the evoked potentials in the thalamus or the midbrain. Mild hypotension was occasionally encountered.

Volatile Agents.—Nineteen cats made up this group. The results are summarized in part in table 2. Although a range of concentrations of each agent was tested, we present only the average changes at one particular concentration for each agent. This was the concentration deemed by observation either to give a maximum depression in the absence of toxic side effects on the cardiovascular system (as with the halogenated drugs) or, when such toxicity was not a factor (as

with the ethers), the greatest of the commonly used clinical concentrations. Examples of the effect of each agent for indicated concentrations are shown in figure 2. *It should be emphasized that all of these agents produced increasing depression of the potentials with increasing concentrations.* No attempt was made to determine the absolute maximum concentrations which could be tolerated by the animals.

DIVINYL ETHER (VINETHENE): Five animals were studied over a range of 4 to 12 per cent concentration. With 8 per cent concentration, the thalamic potential showed beginning depression of amplitude in 4 minutes, progressed to a maximum of 26 per cent below controls

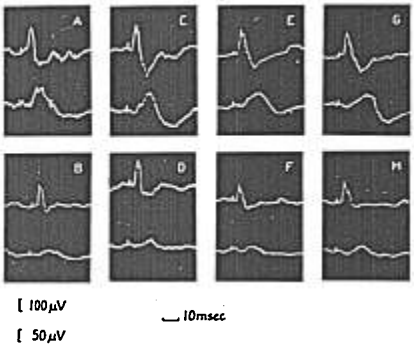

FIG. 2. Recordings of the changes for each of the four volatile anesthetic agents in the cat. The upper tracing of each photograph is from the postero-ventrolateral nucleus of the thalamus, the lower from the midbrain periaqueductal reticular formation at the level of the superior colliculi. A, C, E and G are controls, respectively, for the results following administration of the agents seen directly beneath in B, D, F and H. Shown are the effects, in two different animals, of 13 minutes of diethyl ether 10 per cent (B), 3 minutes of chloroform 2 per cent (D), and in another animal, of 14 minutes of divinyl ether 12 per cent (F), followed, 24 minutes later, with 13 minutes of trichlorethylene 2 per cent (H). The 100-microvolt scale refers to the thalamic tracing in each instance; the 50-microvolt scale refers to the midbrain. Time intervals for all photographs are calibrated to the 10 millisecond scale.

in 10 minutes, and returned to control after 5 minutes of oxygen washout. The midbrain potential showed onset of depression in 2 minutes, reached a maximum of 60 per cent below control in 11 minutes, and returned to control after 10 minutes of washout. There was no change in conduction latency or background activity. Cardiovascular difficulties were not encountered in any concentration up to the maximum of 12 per cent used in this study.

DIETHYL ETHER: Five animals were studied over a range of 5 to 15 per cent concentration. With 10 per cent concentration, the thalamic potential showed beginning depression in 8 minutes, progressed to a maximum of 25 per cent below control at 12 minutes, and returned to

control after 12 minutes of washout. The midbrain potential showed onset of depression in 2 minutes, progressed to a maximum of 75 per cent below control at 11 minutes, and returned to control after 42 minutes. There was no change in conduction latency or background activity. Cardiovascular changes were absent even at 15 per cent concentration.

CHLOROFORM: Four animals were studied over a range of 0.5 to 3.0 per cent concentration. With 2 per cent concentration, the thalamic potential showed beginning depression in 4 minutes, progressed to a maximum of 23 per cent below control at 8 minutes, and returned to control in 9 minutes. The midbrain potential showed onset of depression in 2 minutes, progressed to a maximum of 63 per cent below control at 6 minutes, and returned to control in 11 minutes. Concentrations over 2 per cent invariably resulted in cardiac arrhythmias and hypotension which was marked but which was promptly reversible upon withdrawal of the agent.

TRICHLORETHYLENE (TRILENE): Five animals were studied over a range of 0.5 to 3.0 per cent concentration. With 2 per cent concentration, the thalamic potential showed beginning depression in 5 minutes, progressed to a maximum of 20 per cent below control in 11 minutes, and returned to control in 6 minutes. The midbrain potential showed onset of depression in 1 minute, progressed to a maximum of 40 per cent below control in 7 minutes, and returned to control in 11 minutes. Concentrations over 1 per cent occasionally resulted in cardiac arrythmias but significant hypotension was seldom encountered.

DISCUSSION

There has been considerable controversy as to the effects of the neuromuscular blocking agents on the central nervous system (7, 8). The subcortical regions evaluated in the cat in the manner described above are not affected by these drugs *per se* even in massive intravenous doses many times greater than clinical ranges, provided care is taken to avoid hypotension and hypoxia. It has been pointed out that the administration of *d*-tubocurarine, particularly, is often followed by significant depression of blood pressure and that any one of these agents can produce hypotension, reversible for the most part, by postural augmentation of venous return. These observations are of pharmacologic interest and they are of practical significance to the laboratory worker pursuing studies in which the relaxant drugs are used.

The volatile anesthetic agents depress the thalamic and midbrain evoked potentials in a manner comparable to that previously reported with the gaseous agents (1), differing mainly in a slower onset and a more prolonged effect. With the concentrations studied, both the thalamic and midbrain potentials are depressed, the average for the

former being about 25 per cent, and for the latter about 75 per cent of control amplitude. Even with 15 per cent ether, 12 per cent divinyl ether, and 3 per cent chloroform—the maximum concentrations of these agents used—the midbrain potential never entirely disappeared as it does with comparable concentrations of cyclopropane. It is quite possible that higher concentrations of these volatile agents might result in 100 per cent depression. Also, longer exposure periods to the concentrations studied might result in further depression; however, it appeared that a maximum depression was reached fairly early in our preparations, with no significant change thereafter.

Within the limits of the concentrations of the volatile agents studied, the time from the application of a peripheral nerve stimulus to the subsequent evoked response (latency) did not change. This would intimate no appreciable effect of these drugs on conduction over fiber pathways leading to the two regions under observation, a finding similar to that with the gases. Work by Larrabee and Posternak (9) points to the synapse as the likely site of action of certain general anesthetics. Recent studies by Randt, Collins, Davis and Dillon (10) indicate a differential susceptibility to the gaseous anesthetic agents of afferent systems of different fiber size which may be related to intrinsic variations in transmission in these systems.

Summary

The effect of commonly used muscle relaxants and volatile anesthetics on evoked potentials from the thalamus and the midbrain reticular formation of the cat have been studied.

In 32 animals, it was found that *d*-tubocurarine chloride, gallamine triethiodide, decamethonium bromide, and succinylcholine chloride administered intravenously had no effect, even in large doses, provided hypotension, hypothermia and hypoxia were avoided.

In 19 animals, it was demonstrated that diethyl ether, chloroform, divinyl ether, and trichlorethylene all depressed the amplitude of the evoked responses affecting the midbrain reticular potentials to a greater degree than the thalamic relay evoked response. In the concentrations utilized, the diethyl ether proved the most potent in this regard, followed in order by chloroform, divinyl ether, and trichlorethylene.

In general, the onset of depression was slower and its duration longer with these agents than with the previously reported anesthetic gases. The conduction latency was unaffected. These findings correlate with clinical experience, except that chlorofrom is generally accepted as a more potent agent than ether. However, the difference in this study between the two agents was not significant and, furthermore, it was emphasized that cardiovascular side effects prevented more than brief exposure to chloroform in most instances.

These findings suggest that the volatile agents depress the midbrain

reticular system in a manner similar to anesthetic gases. They lend further support to the concept that the general anesthetic state is associated with a reversible depression of the midbrain ascending reticular system.

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